DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2002D–0307] (formerly 02D–0307)

Guidance for Industry on Potassium Chloride Modified-Release Tablets and Capsules: In Vivo Bioequivalence and In Vitro Dissolution Testing; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a guidance for industry entitled "Potassium Chloride Modified-Release Tablets and Capsules: In Vivo Bioequivalence and In Vitro Dissolution Testing." This guidance document provides recommendations to sponsors of abbreviated new drug applications (ANDAs) on the design of bioequivalence studies for modified-release dosage forms of potassium chloride.

DATES: Submit written or electronic comments on agency guidances at any time.

ADDRESSES: Submit written requests for single copies of this guidance to the Division of Drug Information (HFD–240), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Send one self-addressed adhesive label to assist that office in processing your requests. Submit written comments on the guidance to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to *http:/*

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/www.fda.gov/dockets/ecomments. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the guidance document.

FOR FURTHER INFORMATION CONTACT: Lizzie Sanchez, Center for Drug Evaluation and Research (HFD–650), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–5847.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a guidance for industry entitled "Potassium Chloride Modified-Release Tablets and Capsules: In Vivo Bioequivalence and In Vitro Dissolution Testing." This guidance is intended to provide information to sponsors of ANDAs on the design of bioequivalence studies for modified-release dosage forms of potassium chloride.

A document entitled "Guidance for In Vivo Bioequivalence Study for Slow-Release Potassium Chloride Tablets/Capsules" was issued on May 15, 1987 (1987 guidance), and revised on June 6, 1994 (1994 revision). The guidance was further revised to incorporate FDA's current thinking on the bioequivalence requirements for potassium chloride modified-release products and was issued in draft on August 7, 2002 (2002 draft guidance) (67 FR 51284). Comments were reviewed and incorporated. The most substantive changes made are described in the following paragraphs. Editorial changes were also made and the final guidance is now available.

In the 2002 draft guidance, the agency recommended a three-way crossover design study comparing the reference listed drug (RLD) to both the generic product and a solution of potassium chloride. The 2002 draft guidance also recommended analysis of covariance (ANCOVA) for the pharmacokinetic parameters.

The final guidance provides recommendations for a two-way crossover design comparing the generic product to the RLD. This design is consistent with the 1994 revision, which stated that the potassium chloride solution mentioned in the 1987 guidance was no longer necessary and recommended the use of a two-treatment, two-period, single-dose, fasting study comparing test product with reference product. The FDA determined that the potassium chloride solution arm is not necessary because the objective of the bioequivalence study is to directly compare the rate and extent of potassium absorption from the test product and the reference product. Therefore, the potassium chloride solution arm is not necessary for the test-versus-reference comparison and adds unnecessary complexity to the statistical bioequivalance analysis.

We also have decided not to recommend the use of ANCOVA in the final guidance. Analysis of variance (ANOVA) with baseline correction is adequate for bioequivalence analysis of pharmacokinetic data obtained following oral administration of potassium chloride drug products. The FDA concluded that using ANCOVA with baseline as a covariate to analyze baseline-uncorrected data was not as sensitive to changes in formulation performance as using ANOVA to analyze baseline-corrected data.

The dissolution testing and criteria for waivers on in vivo testing for lower strengths are revised to reflect the changes outlined in the guidance entitled "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations," available on the Internet at *http://www.fda.gov/cder/guidance/index.htm.*

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the agency's

current thinking on studies to demonstrate the bioequivalence of potassium chloride modified-release tablets and capsules. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

II. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments on the guidance at any time. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The guidance and received comments are available for public examination in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

III. Electronic Access

Persons with access to the Internet may obtain the document at either *http://www.fda.gov/cder/guidance/index.htm* or *http://www.fda.gov/ohrms/dockets/default.htm.*

Dated: 10/13/05

October 18, 2005.

Jeffrey Shuren,
Assistant Commissioner for Policy.

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